UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,972	04/07/2006	Takeshi Doi	288989US0PCT	5923

22850 7590 08/27/2008

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER
O'DELL, DAVID K

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
08/27/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/574,972	DOI ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 23-33 are pending.

Priority

3. The English translation and a statement that the translation is accurate required by 37 CFR 1.78(a)(5) has been provided in application 60/510,012 thus priority is granted.

Response to Arguments and Remarks

3. Applicant's representatives arguments filed on May 15, 2008 have been fully considered but they are not persuasive. The sole argument put forth with respect to the rejection under 35 U.S.C. 103 (a) for obviousness, is reproduced below:

"Kodama '169 (U.S. Patent 6,498,169) describes that cyclic amine compounds represented by general formula (1) exhibit inhibitory effects on cell adhesion, and are useful for treating inflammatory diseases (See e.g., abstract and column 1, lines 11-18). It is understood that "cell adhesion," as used in Kodama ' 169, means that activated leukocytes adhere to endothelial cells in inflammatory sites through various cell adhesion molecules, such as ICAM- 1, VCAM-1, E-selectin, LFA-1 and VLA-4, for example (See e.g., column 1, lines 40-64). On the other hand, although Bicknell describes that tumor angiogenesis involves the "alignment" of only endothelial cells into tube-like structures, there is no description about "adhesion" therein.

Accordingly, while a skilled artisan would have reasonably concluded that the cyclic amine compounds described in Kodama '1 69 could inhibit adhesion between the heterogeneous cells of activated leukocytes and endothelial cells in inflammatory sites, a skilled artisan would not have had a reasonable expectation of success that the cyclic amine compounds would inhibit adhesion (not to be confused with alignment, as described in Bicknell) between the homogeneous endothelial cells in the complex process of tumor angiogenesis." (Remakrs pg. 7-8)

Apparently the applicant is suggesting that alignment of endothelial cells in angiogenesis doesn't involve endothelial cell adhesion. It is well understood in the art that cell alignment and angiogenesis in general necessarily involve cell adhesion and the following reference is

submitted to show that in fact when one is speaking of the alignment of endothelial cells and angiogenesis, adherence is necessarily taking place:

"Endothelial cell proliferation is a major component of angiogenesis, but is only one of a series of tasks the endothelial cells must accomplish to form a new capillary blood vessel. In response to angiogenic stimuli, endothelial cells degrade the extracellular matrix (ECM),[1] migrate into the perivascular space, proliferate, and align themselves into patent blood vessels. When sufficient angiogenesis has occurred, the endothelial cells become quiescent and the vessels either remain or regress if no longer needed. **During these events, the endothelial cells must adhere to one another** and to the ECM to construct and extend new microvessels." Joyce Bischoff "Perspectives Series: Cell Adhesion in Vascular Biology Cell Adhesion and Angiogenesis" *Journal of Clinical Investigation* (99) 3, February **1997**, 373–376. (pg. 373 paragraph 2)

The second argument that even though the prior art teaches that the compounds of the instant invention "inhibit adhesion between the heterogeneous cells of activated leukocytes and endothelial cells" they would not be expected to "inhibit adhesion between the homogeneous endothelial cells in the complex process of tumor angiogenesis." is not necessarily relevant since adhesion between leukocytes and endothelial cells alone can in fact be a requirement of angiogenesis as shown by the following citation:

"**However, angiogenesis sometimes depends on the interaction of endothelial cells with other types of cells**, and the roles of cell adhesion molecules in such interaction remain to be studied. It is noteworthy that the in vitro angiogenesis of bovine aortic endothelial cells induced by polymorphonuclear leukocytes requires adhesion of leukocytes to endothelial cells through E-selectin and integrin/intercellular adhesion molecule-1 interaction (44, 45). When added to the coculture of F-2 cells with A431 cells, the anti-sialyl Lex/Lea antibodies as well as anti-β1-integrin antibody significantly inhibited the interaction of endothelial cells with cancer cells. The orderly formation of cancer cell nests surrounded by functional vascular networks of F-2 cells was almost completely inhibited by these antibodies both in vitro and in vivo. **Our results indicated that the interaction of cancer cells with endothelial cells through adhesion molecules such as selectins and integrins is critical for generation of functional vascular networks nourishing cancer cell nests and promoting in vivo growth of tumors.** The novel in vitro and in vivo model experimental systems described here offer a unique opportunity to study direct or indirect interaction between cancer cells and endothelial cells together with the outcome." Tei et. al. "Roles of Cell Adhesion Molecules in Tumor Angiogenesis Induced by

Cotransplantation of Cancer and Endothelial Cells to Nude Rats" CANCER RESEARCH 2002, 62, 6289–6296.

The prior art '169 patent teaches that HUVECs stimulated with the cyctokine TNF-alpha become adherent to U937 cells and that the compounds of the instant invention block this adherence. The HUVECs are epithelial cells widely used in studies of angiogenesis. The U937 cells are lymphatic cancer cells. Clearly given the close connection between angiogenesis and cell adhesion, as shown above only one conclusion can be reached that invention as a whole is obvious over the prior art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 23-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over U. S. patent 6,498,169 (cited on the IDS) in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

A) Determining the scope and contents of the prior art: The '169 patent teaches the elected species of the instant case, moreover the '169 patent also teaches that the elected species and other compounds of the instant case are inhibitors of endothelial cell adhesion (column 118 - 119, Table 1). Bickwell teaches that "alignment of endothelial cells into tube-like structures" or adhesion of these cells to one another, is a key step in angiogenesis. Moreover Bicknell teaches that angiogenesis is important for the growth of solid tumors.

B) Ascertaining the differences between the prior art and the claims at issue.

The process of the instant case involves the "inhibiting angiogenesis" and treating solid tumors with 4-[N-(4-methoxyphenyl)-N-[[5-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl) pyridin-4-yl] methyl] piperidine, while the prior art teaches the inhibition of cell adhesion with 4-[N-(4-methoxyphenyl)-N-[[5-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl) pyridin-4-yl] methyl] piperidine. It goes

without saying that the compounds and their method of administration is identical. It would appear then that the applicant seems to believe that a new property has been discovered.

C) Resolving the level of ordinary skill in the pertinent art: The level of ordinary skill is high. Someone using these compounds would be a medical doctor.

D) Considering objective evidence present in the application indicating obviousness or nonobviousness: One of ordinary skill would have realized based on the teachings of Bicknell et. al. that inhibitors of endothelial cell adhesion would also find use as angiogenesis inhibitors and for the treatment of solid tumors. A person of ordinary skill in the art would have been motivated to do so based on the desire to treat tumors which are not desirable tissues

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 23-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-17 of U.S. Patent No. 6,395,753 in view of

Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current claims although drawn to "inhibiting angiogenesis" and methods of treating diseases caused by angiogenesis the '753 patent, covers methods of treating diseases caused by cell adhesion with the same compounds. See the 103(a) rejection above for a detailed discussion.

6. Claims 23-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15-20 of U.S. Patent No. 6,498,169 in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current claims although drawn to "inhibiting angiogenesis" and methods of treating diseases caused by angiogenesis the '169 patent, covers methods of treating diseases caused by cell adhesion with the same compounds. See the 103(a) rejection above for a detailed discussion.

7. Claims 23-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3 of U.S. Patent No. 6,605,620, in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current claims although drawn to "inhibiting angiogenesis" and methods of treating diseases caused by angiogenesis the '620 patent, covers methods of treating diseases caused by cell adhesion with the same compounds. See the 103(a) rejection above for a detailed discussion.

8. Claims 23-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-17 of U.S. Patent No. 6,867,221 in view of Bickwell et. al. *Tumour Angiogenesis* **1997**, Oxford Univ. pg. 19. Although the conflicting

claims are not identical, they are not patentably distinct from each other because the current claims although drawn to "inhibiting angiogenesis" and methods of treating diseases caused by angiogenesis the '221 patent, covers methods of treating diseases caused by cell adhesion with the same compounds. See the 103(a) rejection above for a detailed discussion.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625